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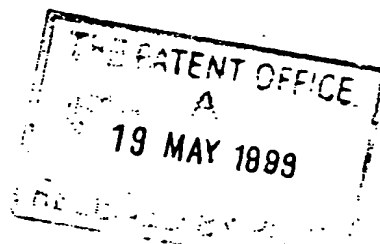
Dated

6th June 2000

2

# Request for grant of a patent

(See the notes on the back of this form. You can also get an explanatory leaflet from the Patent Office to help you fill in this form)



The Patent Office

Cardiff Road  
Newport  
Gwent NP9 1RH

1. Your reference

MGH/MG/P08737GB

2. Patent application number

(The Patent Office will fill in this part)

9911546.1

3. Full name, address and postcode of the or of each applicant (underline all surnames)

CORE TECHNOLOGIES LIMITED  
Block 8, Unit 2  
Moorfield Industrial Estate  
Moorfield  
KILMARNOCK KA2 0BA

Patents ADP number (if you know it)

If the applicant is a corporate body, give the country/state of its incorporation

UK

7399504-001

4. Title of the invention

RELEASE OF POORLY SOLUBLE AGENTS

5. Name of your agent (if you have one)

"Address for service" in the United Kingdom to which all correspondence should be sent (including the postcode)

CRUIKSHANK & FAIRWEATHER  
19 Royal Exchange Square  
GLASGOW G1 3AE

Patents ADP number (if you know it)

547002

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and (if you know it) the or each application number

Country

Priority application number  
(if you know it)

Date of filing  
(day / month / year)

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application

Date of filing  
(day / month / year)

8. Is a statement of inventorship and of right to grant of a patent required in support of this request? (Answer 'Yes' if:

a) any applicant named in part 3 is not an inventor, or

b) there is an inventor who is not named as an applicant, or

c) any named applicant is a corporate body.

See note (d))

# Patents Form 1/77

9. Enter the number of sheets for any of the following items you are filing with this form. Do not count copies of the same document

## Continuation sheets of this form

Description	10	(3)
Claim(s)	1	
Abstract	-	
Drawing(s)	2	+2

10. If you are also filing any of the following, state how many against each item.

## Priority documents

Translations of priority documents

Statement of inventorship and right to grant of a patent (*Patents Form 7/77*)

Request for preliminary examination and search (*Patents Form 9/77*)

Request for substantive examination (*Patents Form 10/77*)

Any other documents  
(please specify)

11. I/We request the grant of a patent on the basis of this application.

Signature

Date

CRUIKSHANK & FAIRWEATHER

18/05/99

12. Name and daytime telephone number of person to contact in the United Kingdom

## Warning

After an application for a patent has been filed, the Comptroller of the Patent Office will consider whether publication or communication of the invention should be prohibited or restricted under Section 22 of the Patents Act 1977. You will be informed if it is necessary to prohibit or restrict your invention in this way. Furthermore, if you live in the United Kingdom, Section 23 of the Patents Act 1977 stops you from applying for a patent abroad without first getting written permission from the Patent Office unless an application has been filed at least 6 weeks beforehand in the United Kingdom for a patent for the same invention and either no direction prohibiting publication or communication has been given, or any such direction has been revoked.

## Notes

- If you need help to fill in this form or you have any questions, please contact the Patent Office on 0645 500505.
- Write your answers in capital letters using black ink or you may type them.
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- If you have answered 'Yes' Patents Form 7/77 will need to be filed.
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### RELEASE OF POORLY SOLUBLE AGENTS

The present invention relates to a controlled release pellet composition for delivering a poorly soluble pharmaceutically active agent in a controlled manner over an extended period of time, typically over a period of 24 hours. The formulation is intended to enhance and control the release rate of agents, such as nifedipine, which are otherwise only poorly soluble in aqueous liquids.

Enhancement of the rate of dissolution of nifedipine has been the subject of research. Shu-Yang Yen et al (Drug Development and Industrial Pharmacy, 23(3), 313-317 (1997)) report that dissolution enhancement of nifedipine may be achieved by using super-disintegrants such as sodium starch glycolate, crospovidone and croscarmellose sodium. Nifedipine was formed into uncoated granules and tablets. Substantial dissolution was achieved within about 60 minutes. However, there is no report on the controlled release properties of these formulations.

Chowdray KPR and G. Girija Sankar (Drug Development and Industrial Pharmacy 23(3), 325-330 (1997)) describe the microencapsulation of nifedipine with Eudragit RL PM (a water-insoluble acrylic polymer). The core contained in addition to nifedipine, hydroxypropylmethyl cellulose and microcrystalline cellulose. Release of nifedipine over a period of 12 hours was reported.

The bioavailability of cores containing nifedipine and hydroxypropylmethyl cellulose phthalate together with

methacrylic acid-methacrylic acid methyl ester copolymer (Eudragit L) was investigated in animal studies reported in A. Hasegawa et al (Chem. Pharm. Bull.33(1) 388-391 (1985)).

US Patent 5,051,263 (Barry et al) describes a sustained release granule formulation comprising a core containing a poorly soluble active agent such as nifedipine, the core being coated with a mixture comprising a water insoluble but water swellable acrylic polymer and a water-soluble hydroxylated cellulose derivative. The core comprises the active agent, a carbomer (generic name for carboxypolymethylene) and microcrystalline cellulose.

It is an object of the present invention to provide improved controlled release formulations for use with pharmaceutical agents which are poorly soluble in water.

The present invention is based on the surprising discovery that the incorporation of a polyethylene glycol into the core improves the controlled release properties.

Thus, the present invention provides a controlled release pellet, which comprises:

- a core containing a poorly soluble pharmaceutically active agent and a polyethylene glycol;
- a coating around the core and comprising a water-soluble cellulose and a water-insoluble acrylic polymer.

The core may be formed in conventional manner as set out in, for example, patent specifications US 4,900,558, US 5,051,363 and US 5,055,306.

The core may also contain a disintegrant such as

sodium starch glycolate, croscopovidone and croscarmellose sodium. The amount of disintegrant is generally in the region 0-10% by weight, particularly 1-5% by weight.

In addition to the pharmaceutically active agent and the polyethylene glycol, the core generally also comprises a carrier such as a water-insoluble swellable cellulose, such as microcrystalline cellulose. A pH modifier, such as sodium bicarbonate, dibasic calcium phosphate, citric acid or tris(hydroxymethyl)aminomethane (Tris), may be included in the core to buffer the core to a pH which gives preferred dissolution characteristics for the active agent. This may be used to improve the solubility of certain poorly soluble active agents. Where the pellets are to be formed into tablets, a proportion of a water insoluble or pH sensitive acrylic polymer may also be included in the core to maintain the preferred dissolution rate after compression. The amount of carrier in the core is preferably in the region 0-70% by weight, particularly 10-60% by weight. The amount of water insoluble acrylic polymer in the core is preferably in the region 0-50% by weight, particularly 10-30% by weight.

Generally, the cores have a size in the range 0.5 to 2.0mm, preferably 0.5 to 1.4mm.

The polyethylene glycol which is included in the core has been found to enhance the dissolution rate of the poorly soluble active agent and also to assist in providing controlled release. Polyethylene glycols are well known in the art and include a repeating  $-(CH_2CH_2O)-$  group with

various terminal groups. Polyethylene glycols are categorised according to their nominal molecular weight and in the present invention nominal molecular weights of 1000 to 8000 (i.e. PEG 1000 to PEG 8000) are preferred. The polyethylene glycol is generally a solid at room temperature but is melted prior to formulation. Usually, the amount of polyethylene glycol in the core is in the range 5-50% by weight, particularly 10-30% by weight.

The amount of polyethylene glycol required is to an extent dependent on the amount of active agent present and it is preferred that the ratio of polyethylene glycol to active agent lies in the range 0.5 to 2.0:1 by weight.

The poorly soluble pharmaceutically active agent is typically nifedipine or other poorly soluble active agent such as glibenclimide or griseofulvin. The active agent is generally present in an amount of 1-90% by weight, typically 5-70% by weight of the core weight. The solubility of the poorly soluble active agent is generally less than 1mg/ml at room temperature and pH7. The solubility of nifedipine is less than 0.1mg/ml.

The coating around the core controls release of the active agent from the core itself (in conjunction with the properties of the core matrix). The coating comprises a mixture of a water soluble cellulose and a water insoluble acrylic polymer. The ratio of water insoluble agent to water soluble agent is a factor controlling the release rate and the ratio is generally in the range of 1:1 to 10:1, generally 5:3 to 5:1 respectively. The water



insoluble acrylic polymer is preferably neutral and may comprise a homopolymer or copolymer, for instance of acrylic acid esters or methacrylic acid esters. Usually, the acrylic polymer is provided as an aqueous dispersion. A particularly suitable acrylic polymer is sold under the trademark Eudragit NE30D and comprises a copolymer of acrylic and methacrylic acid esters and is usually supplied as an aqueous dispersion containing approximately 30% by weight solids.

The water soluble cellulose may be a hydroxylated cellulose derivative, such as hydroxypropylmethyl cellulose, typically having a degree of substitution of 28-30% of methoxy groups and 7-12% of hydroxypropyl groups. Hydroxypropyl, hydroxyethyl or hydroxymethyl celluloses may also be used.

The coating preferably comprises from 3-40% by weight, preferably 5-25% by weight of the pellet.

Since nifedipine is known to interact with food in the stomach, in a particularly preferred embodiment the pellet is further coated with an enteric coating. Enteric coatings are well known in the art and typically comprise an acid-resistant agent.

If necessary, the pellets of the present invention may be formed into tablets together with conventional tableting agents.

Embodiments of the present invention will now be described by way of example only.

Example 1

Cores containing nifedipine and polyethylene glycol (PEG4000) were prepared as described below having the formulations set out in Table 1.

Table 1 (Core Formulation)

Material	Quantity (g)
Nifedipine USP (surface area of approx. 0.8m <sup>2</sup> /g)	225.3
Polyethylene Glycol 4000 USPNF	225.0
Microcrystalline Cellulose USPNF (Avicel PH101)	530.2
Croscarmellose Sodium USPNF (Ac-Di-Sol)	20.1
Purified Water	405.1

The cores were coated with two coating suspensions. The first coating suspension functioned as a release rate controlling coat and had the formulation as set out in Table 2. The coating suspension contained 20%w/w solid material and the weight of suspension added was equivalent to 5% of the core weight.

Table 2- First Coating Suspension (Release Rate Controlling Coat)

Material	Quantity (g)
Poly(ethylacrylate, Methylmethacrylate) 2:1 (Eudragit NE30D)	293.8
Hydroxypropylmethylcellulose (Pharmacoat 603)	53.1
Talc	58.9
Purified Water	596.9

A second (enteric) coating was also applied. The second coating suspension is shown in Table 3 and contained 20%w/w solid material. The weight of suspension added was equivalent to 10% of the core weight.

Table 3 - Second Coating Suspension (Enteric Coat)

Material	Quantity (g)
Poly(methacrylic acid, ethylacrylate) 1:1 (Eudragit L30D-55)	416.8
Talc	62.6
Triethyl Citrate	12.5
Purified Water	508.7

(a) Core Production

A 1kg batch of cores (batch 5507:00198) was produced as follows. Molten PEG4000 was weighed into a pre-heated mixing bowl of a Erweka AR401 planetary mixer at a temperature of 90°C. Nifedipine was added over a period of 1 to 2 minutes at a mixing speed of approximately 180rpm and the mixture mixed for a further 2 to 3 minutes. Ac-Di-

Sol was dispersed in the batch quantity of water and added to the nifedipine/PEG4000 mixture over 4 minutes at 100rpm. Avicel PH101 was added and mixed over a period of 7 to 8 minutes at 100rpm to produce a wet mass. The wet mass was covered and allowed to cool to 29°C. Then the wet mass was extruded through a 0.8mm screen of a Niro Fielder E140 extruder at a feeder speed of approximately 45rpm and an impeller speed of approximately 30rpm. The extrudate was collected and spheronised for 12.5 minutes in a Niro Fielder S450 spheroniser at approximately 400rpm. The spheres were collected and dried at approximately 55°C in an Aeromatic Fielder Strea 1 fluid bed drier. The dried cores were sieved to between 0.5 and 1.4mm to remove fines and large agglomerates.

#### (b) Coated Pellet Production

A batch size of 600g of the cores was coated to produce pellets (batch 5509:00198) as follows. The first coating suspension was prepared by dissolving hydroxypropylmethyl cellulose (Pharmacoat 603) in approximately 450g of purified water and mixing with a low shear mixer for approximately 2 hours. Talc was added and dispersed using a Silverson SL2 hi-shear mixer for approximately 30 mins. This mixture was added to the Eudragit NE30D, made up to 1000g with the remaining purified water and stirred for 20 minutes at approximately 350rpm using a Heidolph RZR2051 mixer until uniform.

The second coating suspension was prepared by

dispersing the triethyl citrate and talc in approximately 300g of purified water using a Silverson SL2 hi-shear mixer for 7 minutes, adding to Eudragit L30D-55 and the remaining water and stirring at approximately 350rpm for 6 minutes using a Heidolph RZR2051 mixer until uniform.

The first coating suspension was added to the batch of cores in an Aeromatic Fielder Strea 1 fluid bed drier using a 0.8mm spray gun nozzle at 8g/min, 1 bar atomising pressure, inlet temperature 35°C and airflow of 90m<sup>3</sup>/hr to form a first coat. The second coating suspension was added immediately thereafter using a 1.1mm spray gun nozzle at approximately 11g/min 1 bar atomising pressure, inlet temperature 35°C and airflow of approximately 100m<sup>3</sup>/hr to form a second coat. The coated cores were placed in an LTE Vulcan 150 oven to cure at approximately 45°C for approximately 20 hours. The coated cores were sieved through a 1.4mm screen to remove agglomerates. The pellets so produced were then stored.

#### (c) Release Profiles

Figure 1 shows the release profile of the coated core of the invention in 900ml of a dissolution medium containing 1% sodium lauryl sulphate and 1% propanediol in simulated gastric fluid. It will be noted that there is good controlled release over the 24 hour period shown.

Example 2 (Comparison)

For comparison purposes, four batches of uncoated nifedipine-containing cores were prepared as in Example 1 having the composition set out in Table 4.

Table 4 (uncoated cores)

Material Batch	Content (g)			
	DNIF97/004	DNIF97/041	DNIF97/043	DNIF98/023
Nifedipine	240.6	225.7	200.9	490.3
Molten PEG 4000	0	225.5	250.3	0
Ac-Di-Sol	0	20.2	0	19.9
Avicel PH101	959.8	529.9	550.7	490.3
Water	1080.0	341.4	321.0	793.8

The formulation DNIF97/041 is substantially the same as the core of Example 1.

Figure 2 shows the release profiles in vitro. It can be seen that the presence of both the polyethylene glycol and the croscarmellose sodium (Ac-Di-Sol) enhance the release rate of nifedipine. Both of these additives are preferred to provide a sufficiently fast dissolution rate of the uncoated pellet cores such that control can be exercised over the final release rate by addition of a rate controlling coating.

The following are trademarks: Avicel, Ac-Di-Sol, Eudragit and Pharmacoat.

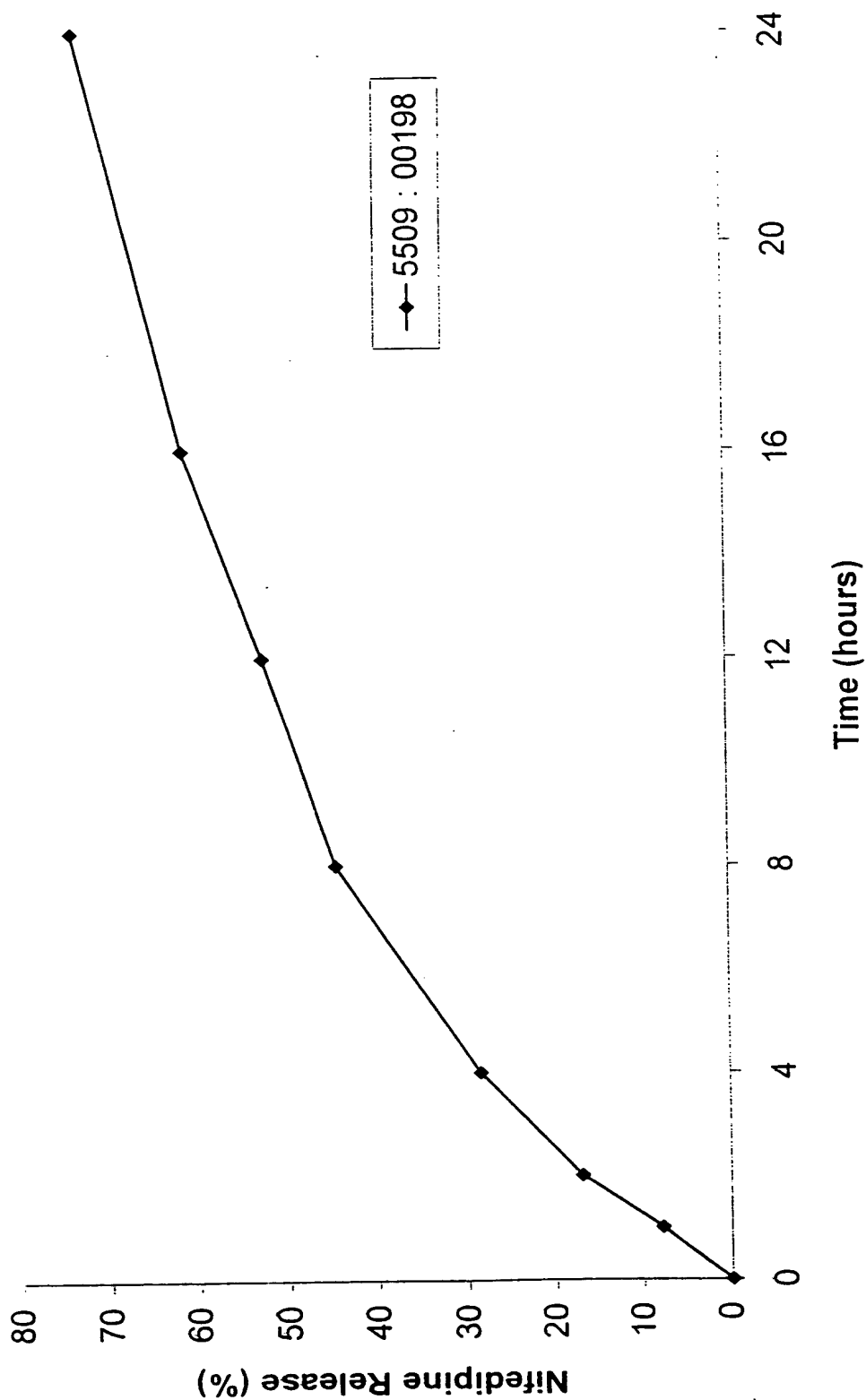
CLAIMS

1. A controlled release pellet, which comprises:
  - a core containing a poorly soluble pharmaceutically active agent and a polyethylene glycol;
  - a coating around the core and comprising a water soluble cellulose and a water insoluble acrylic polymer.



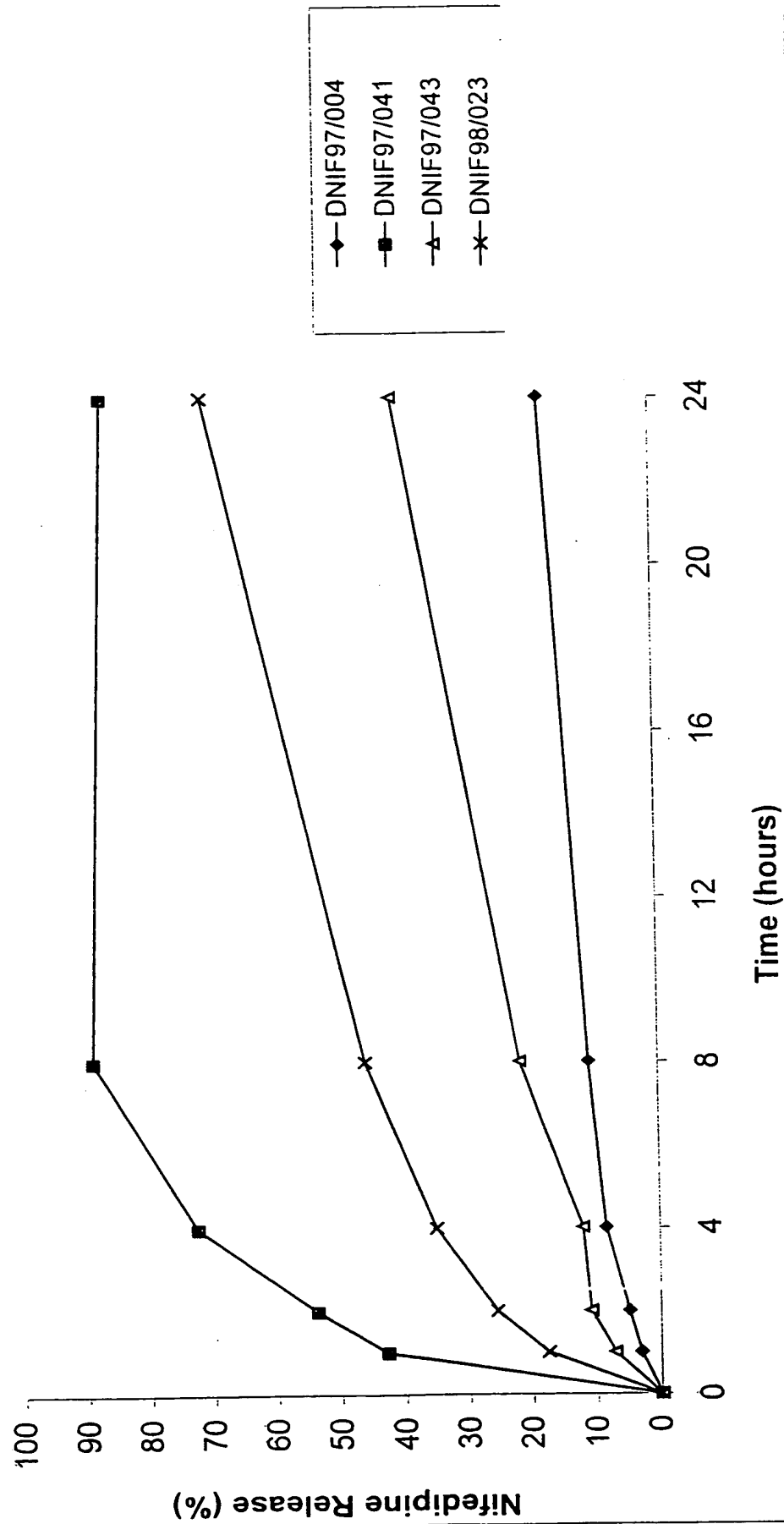


Figure 1  
Release of Coated Nifedipine OSAT Pellet Batch 5509 : 00198





**Figure 2**  
Release Profile of 4 Uncoated Nifedipine OSAT Pellet Batches With or Without  
PEG4000 and/or Ac-Di-Sol



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